Meta-Analyses of Septal Reduction Therapies for Obstructive Hypertrophic Cardiomyopathy
Comparative Rates of Overall Mortality and Sudden Cardiac Death After Treatment

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Methods and Results—Systematic reviews for ASA and surgical myectomy were performed. Study selection and data extraction were completed independently by 2 investigators. Comparative data analyses were completed using a random effects model and regression analysis. Kappa statistics for agreement on initial study inclusion were high for both ASA (0.78; 95% CI, 0.68 to 0.88) and surgical myectomy studies (0.95; 95% CI, 0.84 to 1.0). Nineteen ASA studies (2207 patients) and 8 surgical myectomy studies (1887 patients) were included. Median follow-up was shorter for ASA than for myectomy studies (51 versus 1266 patient-years; \(P<0.001\)). For ASA and surgical myectomy, unadjusted rates (events/patient-years) of all-cause mortality (0.021 versus 0.018, respectively; \(P=0.37\)) and SCD (0.004 versus 0.003, respectively; \(P=0.36\)) were similar. Patients treated with ASA were older (weighted mean, 55 versus 44 years; \(P<0.001\)) and had less septal hypertrophy (weighted mean, 21 versus 23 mm; \(P<0.001\)) compared with those treated with myectomy. After adjustment for available baseline characteristics, odds ratios for treatment effect on all-cause mortality and SCD were 0.28 (95% CI, 0.16 to 0.46) and 0.32 (95% CI, 0.11 to 0.97), respectively, favoring ASA.

Conclusions—Rates of all-cause mortality and SCD after both ASA and surgical myectomy were similarly low. Adjusted for baseline characteristics, the odds ratios for treatment effect on all-cause mortality and SCD were lower in ASA cohorts compared with surgical myectomy cohorts. (Circ Cardiovasc Interv. 2010;3:97-104.)

Key Words: hypertrophic cardiomyopathy ■ septal ablation ■ myectomy ■ meta-analysis

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular disease and the most common cause of sudden cardiac death (SCD) in young people. In more than two thirds of patients with HCM, significant left ventricular outflow tract (LVOT) obstruction is present either at rest or with exercise. In a subset of these patients, LVOT obstruction causes severe symptoms despite optimal medical therapy. For \(\approx 50\) years, the definitive treatment for medically refractory symptoms of the obstructive form of HCM has been surgical myectomy. In 1994, alcohol septal ablation (ASA) was introduced as a less invasive means of septal reduction. Unlike surgical myectomy in which a hypertrophied region of septal myocardium is resected, ASA results in a focal myocardial infarction with replacement of myocardium by fibrosis. Several cases of SCD after ASA have been reported, raising concern that this iatrogenic scar may act as an arrhythmogenic substrate that potentiates the predisposition to ventricular tachyarrhythmia and SCD in patients with obstructive HCM.

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Editorial see p 91
Clinical Perspective on p 104

In 2006, the American College of Cardiology-European Society of Cardiology Consensus Document on HCM stated that “a predominating concern raised with respect to ASA is the potential long-term risk for arrhythmia-related cardiac events (including SCD) directly attributable to the procedure.” Despite thousands of ASA procedures performed globally to date, the possibility of an increased risk of sudden death after ASA compared with surgical myectomy has been neither substantiated nor refuted. The objective of this study was to compare overall survival and SCD rates after ASA or surgical myectomy.
Selection of ASA Studies

Unlimited searches of PubMed for “alcohol septal ablation,” “transcoronary ablation of septal hypertrophy,” and “nonsurgical septal reduction OR nonsurgical septal reduction” yielded 320 unique references on April 4, 2009. Predetermined inclusion and exclusion criteria (Table 1) were applied to each of the 320 references by 2 independent reviewers.

After the initial review, Kappa for agreement on inclusion or exclusion was 0.78 (95% CI, 0.68 to 0.88). Disagreements were resolved by consensus, and a total of 48 publications were selected for further evaluation. A detailed review of study authors, dates, locations, and individual patient outcomes was used to identify redundancy, and 29 publications were excluded. After additional examination of available studies, 19 ASA-related publications ultimately were included (Figure 1 and online-only Data Supplement references) in the analysis.

Selection of Myectomy Studies

Unlimited searches of PubMed for “myectomy AND hypertrophic” and “myomectomy AND hypertrophic” yielded 475 references on April 4, 2009. Predetermined inclusion and exclusion criteria (Table 2) were applied to each of the 475 references by 2 independent reviewers.

After the initial review, Kappa for agreement on inclusion or exclusion was 0.95 (95% CI, 0.84 to 1.0). Disagreements were resolved by consensus, and a total of 9 publications were selected for initial inclusion. A detailed review of study authors, dates, and locations was used to exclude redundancy, and 1 publication was excluded. All authors reported the quality of clinical follow-up, and there were no changes during the period of data extraction and review (Figure 1).

Data Extraction

All data were independently extracted by 2 investigators, and the disagreements were resolved by consensus. Continuous variables were extracted as medians or weighted means for each study’s population, and dichotomous variables were extracted in absolute numbers.

Baseline patient characteristics of interest included age, sex, LVOT gradient (by echocardiography), septal wall thickness, New York Heart Association (NYHA) functional class, and the presence or absence of generally accepted risk factors for SCD in HCM. The primary outcomes of interest were all-cause and sudden mortality. All-cause mortality was defined as any death, and SCD was defined as death definitively or presumably (as defined by the primary study) caused by primary ventricular tachyarrhythmia. Appropriate implantable cardioverter defibrillator (ICD) interventions were counted once as SCD. Other postprocedural data, including permanent pacemaker and ICD implantations; appropriate ICD interventions; and aggregate LVOT gradients, septal wall thickness, peak creatine kinase levels, and NYHA functional classes for each study’s population also were extracted.

Statistical Analysis

Descriptive statistics of patients before the intervention included medians and means (weighted for patient-years of follow-up), with comparisons using either parametric or nonparametric tests, depending on whether the findings were normally distributed. Secondary outcomes were described with medians and interquartile ranges.

The number of all-cause deaths among the cohorts was skewed toward a small number of events. To determine the weighted mean mortality rates of the cohorts, the mortality rates (both all-cause and sudden) were normalized by taking the log (mortality rate) after adding 0.5 deaths to the studies with 0 deaths. Regression analyses were performed using a Poisson regression model to assess the impact of the following baseline variables identified a priori as potential confounders of the treatment effect on the actual number of deaths: age, septal wall thickness by echocardiography, LVOT gradient by Doppler echocardiography, and NYHA functional class. The selection of these variables was based on assumptions that they would be known to a physician recommending septal reduction therapy, may plausibly be associated with mortality, and could affect the treatment decision. Syncope was not consistently reported as a risk factor across studies and was, therefore, not included in the models. The regression model was performed with a backward selection.
process using the Proc GENMOD routine in SAS Enterprise Edition 4.0. The final model produced an expected value for the ln (mortality rate in patient-years). Each model was tested to make sure that the Poisson distribution fit the data. Heterogeneity was assessed with a random effects measure, and publication bias was evaluated using the Begg and Mazumdar rank correlation test and Egger’s regression intercept (Comprehensive Meta Analysis version 2.2.046).

Results

Study Characteristics

Characteristics of the ASA and myectomy cohorts are shown in Table 3. Surgical myectomy results were re-ported for 1887 patients from 1963 to 2005, and ASA results were reported for 2207 patients from 1996 to 2007. The median duration of follow-up after surgical myectomy was substantially longer than after ASA (1266 versus 51 patient-years, respectively; \( P<0.001 \)).

Baseline Patient Characteristics

Baseline patient data are summarized in Table 4. Studies of surgical myectomy included younger patients than the studies of ASA (weighted mean age, 44 versus 55 years, respectively; \( P<0.001 \)). The weighted mean for NYHA class was identical (2.8) in the 2 groups. The myectomy cohorts had a lower median LVOT gradient than the ASA cohorts, but the difference was not statistically significant (67 versus 77 mm Hg, respectively; \( P=0.13 \)). Although the unadjusted mean septal wall thicknesses were not statistically different, the myectomy studies contributed patients with greater septal thicknesses than did the ASA studies (weighted mean, 23 versus 21 mm, respectively; \( P<0.001 \)) when weighted for patient-years of follow-up.

Across all studies, there was a correlation between age and NYHA class (Spearman \( \rho=0.46 \), \( P=0.06 \)). There were no other significant correlations among age, septal wall thickness, LVOT gradient, or NYHA class (\( P>0.13 \) for all
remaining correlations). Other historical features, including extreme hypertrophy, nonsustained ventricular tachycardia, abnormal blood pressure response to exercise, and family history of SCD, were reported in a minority of studies and, therefore, are not shown or analyzed.

**Outcomes**

In myectomy cohorts, there were 250 all-cause deaths and 45 SCD events reported during follow-up; among ASA cohorts, there were 121 all-cause deaths and 26 SCD events. Weighted for patient-years of follow-up, the all-cause and sudden mortality rates after surgical myectomy and ASA were nearly identical (Table 5; Figure 2A and 2B).

As shown in Table 6, residual LVOT gradients and rates of new pacemaker implantation were higher after ASA than after myectomy. NYHA functional class, septal thickness, and prevalence of ICD therapy were similar after septal reduction therapy.

### Regression Analyses

**All-Cause Mortality**

A regression model using assigned treatment with baseline age, septal wall thickness by echocardiography, and NYHA class showed an acceptable fit to the data ($\chi^2=13.3, df=15, P=0.58$ for goodness of fit; see Equation 1). Cohorts treated with ASA ($\beta=-1.3; 95\% CI, −1.8 to −0.7; P<0.0001$).

### Table 5. Primary Outcomes: All-Cause Mortality and SCD Rates

<table>
<thead>
<tr>
<th></th>
<th>Surgical Myectomy % per Patient-Year, Weighted Mean (95% CI)</th>
<th>ASA % per Patient-Year, Weighted Mean (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality rate</td>
<td>1.8 (1.2–2.6)</td>
<td>2.1 (1.7–2.7)</td>
<td>0.37</td>
</tr>
<tr>
<td>SCD rate</td>
<td>0.3 (0.2–0.6)</td>
<td>0.4 (0.3–0.6)</td>
<td>0.36</td>
</tr>
</tbody>
</table>
cohorts with younger patients (β=0.027; 95% CI, 0.001 to 0.05; P=0.04), cohorts with greater preprocedural septal wall thickness (β=−0.45; 95% CI, −0.59 to −0.31; P<0.001), and cohorts with lower NYHA class (β=1.4; 95% CI, 0.57 to 2.2; P<0.001) had lower all-cause mortality rates. LVOT gradient was not significantly related to mortality across cohorts (P=0.22). There were no quadratic or interaction effects (P=0.89 when testing all possible combinations). The regression model for all-cause mortality is calculated as follows:

\[
\ln(\text{all-cause mortality rate, patient-years}) = 1.4 - 1.3 \times (\text{septal ablation} = 1, \text{myectomy} = 0) + (0.027 \times \text{age, years}) - (0.45 \times \text{baseline septal wall thickness, mm}) + (1.4 \times \text{NYHA class})
\]

SCD

Backward elimination of age (P=0.62) and LVOT gradient (P=0.14) resulted in a regression model that showed an acceptable fit to the data (\(\chi^2=12, df=16, P=0.75\) for goodness of fit; see Equation 2). Cohorts treated with ASA (β=−1.1; 95% CI, −2.2 to −0.3; P=0.04), cohorts with greater preprocedural septal wall thickness (β=−0.55; 95% CI, −0.88 to −0.21; P<0.001), and cohorts with lower NYHA class (β=3.8; 95% CI, 1.8 to 5.8; P<0.001) had lower SCD rates. There were no quadratic or interaction effects (P=0.37). The regression model for sudden death is calculated as follows:

\[
\ln(\text{all-cause mortality rate, patient-years}) = -4.0 - 1.1 \times (\text{septal ablation} = 1, \text{myectomy} = 0) - (0.55 \times \text{baseline septal wall thickness, mm}) + (3.8 \times \text{NYHA class})
\]

After adjustment for available baseline characteristics, the odds ratios for treatment effect on all-cause mortality and SCD were 0.28 (95% CI 0.16–0.46) and 0.32 (95% CI 0.11–0.97), respectively, favoring ASA.

Publication Bias and Heterogeneity

The results showed heterogeneity for all-cause mortality in the myectomy studies (P<0.01, \(I^2=83\%\)) but less heterogeneity in the ASA cohorts (P=0.12, \(I^2=29\%\)). A similar
pattern was seen for SCD with heterogeneity in the myectomy studies ($P=0.01$, $I^2=61\%$) but no heterogeneity for ASA ($P=0.80$, $I^2=0\%$).

Among myectomy cohorts, publication bias was suggested for all-cause mortality (Begg and Mazumdar rank correlation test, one-sided $P=0.03$; Egger’s regression intercept, $P=0.004$). For SCD, the statistical tests for the presence of publication bias were not consistent for myectomy (Begg and Mazumdar rank correlation test, one-sided $P=0.27$; Egger’s regression intercept, $P=0.003$). Among ASA cohorts, publication bias was present for both all-cause mortality (Begg and Mazumdar rank correlation test, one-sided $P=0.07$; Egger’s regression intercept, $P=0.02$) and SCD (Begg and Mazumdar rank correlation test, one-sided $P=0.06$; Egger’s regression intercept, $P<0.001$).

Because the absolute mortality rates were low, the impact of publication bias on the end points was assessed. The trim and fill procedure takes the funnel plot for publication bias and imputes missing studies based on the distribution of the known studies. There were no missing studies suggested for all-cause mortality among myectomy studies. For SCD, correcting for missing, small studies would have decreased the mortality rate by 0.002 deaths per patient-year compared with the observed value. For ASA, correcting for missing small studies decreased the all-cause mortality rate by 0.002 deaths per patient-year and lowered the SCD rate by $<0.001$ deaths per patient-year compared with the observed values.

Because inclusion criteria for the sample sizes were different for myectomy versus ASA studies, the analyses were repeated using all the myectomy studies and the 10 largest ASA studies. With this lower-powered analysis, the results showed similar effects and statistical significance for all-cause mortality; for SCD, the estimates approximated each other, with a trend toward fewer sudden deaths in ASA cohorts ($\beta=-1.1$; $P=0.07$).

Discussion

In these systematic reviews of septal reduction therapy for obstructive HCM, rates of all-cause mortality and SCD after ASA were found to be similar to surgical myectomy across observational cohorts of treated patients. The mean rates of overall mortality and SCD were low following both septal reduction therapies. However, after adjustment for available baseline characteristics, the odds ratios for treatment effect on all-cause mortality and SCD were lower in ASA cohorts compared with surgical myectomy cohorts, with shorter duration of follow-up in the ASA cohorts. In light of the rapid, global adoption of the ASA procedure and the strong influence of patient preference on choice of septal reduction therapy, these findings may inform physicians and patients regarding risks of adverse events after these interventions.

All candidates for septal reduction therapy have significant LVOT obstruction and symptoms refractory to medical therapy. Our comparative analyses confirm that both ASA and surgical myectomy effectively reduced LVOT obstruction and improved symptoms across the cohorts. Previous studies have compared the procedures for these efficacy end points using matched cohorts of patients, with similar findings. The annual rates of mortality and SCD should be considered in the context of previously reported rates in treated and untreated patients with HCM. Patients with HCM generally have a low annual rate of overall mortality and SCD (1.3% and 0.7% per year, respectively). Patients with HCM and risk factors for SCD who receive ICDs for primary prevention experience a rate of aborted SCD or appropriate ICD discharges of 3.6% per year. This rate of aborted SCD also has been evaluated after septal reduction therapies for obstructive HCM. In a study of patients with HCM who were treated with septal myectomy, the rate of ICD discharges was 0.24% per year compared with 4.3% per year in the untreated patients with HCM. In a cohort of 67 patients with HCM with histories of septal reduction and ICDs for primary or secondary prevention of SCD, the rate of appropriate ICD discharges after ASA was 10.3% per year compared with 2.6% per year after surgical myectomy. Among the cohorts included in the current meta-analyses, a low percentage of patients had ICDs in follow-up, which is consistent with a low risk of SCD and expected rates of overall mortality and SCD similar to a nonreferral population with HCM.

A randomized trial of septal reduction therapies would ideally evaluate long-term efficacy and safety outcomes, but no studies have been performed to date. There are substantial barriers to the completion of such a study. Consequently, observational data, with their inherent biases of patient selection and center and operator experience, offer the only available insight into mortality rates after septal reduction therapies. The all-cause mortality and SCD rates after ASA or surgical myectomy were nearly identical in this analysis, despite the presence of several factors that may have led to an underestimation of mortality rates after surgical myectomy. The inclusion and exclusion criteria were designed such that all of the surgical myectomy centers were experienced and recognized centers, yet some of the ASA centers were relatively inexperienced. Cohorts treated during the early experience with ASA were included, though greater operator experience, the routine use of myocardial contrast echocardiography, and the trend toward use of smaller volumes of ethanol theoretically may reduce mortality risk after ASA in more contemporary cohorts. Conversely, cohorts from the earlier eras of surgical myectomy also were included, and improvements in operative techniques may have reduced surgical mortality rates. Although publication bias is suggested, the effect on mortality rates is likely small and biased toward a trivial overestimate of all-cause mortality and SCD rates.

Differences in the baseline characteristics of myectomy and ASA cohorts also may influence outcomes. Adjustment for available variables that may have prognostic influence resulted in a significantly lower overall mortality for ASA-treated cohorts than for myectomy-treated cohorts. However, this adjustment cannot account for other potential confounders or differences in cohorts, which may contribute to outcome independently of the septal reduction strategy. Indeed, the baseline characteristics of the cohorts suggest that patients treated with myectomy may have had a more malignant clinical course or phenotype, as these cohorts were significantly younger and had more hypertrophy than the
ASA-treated cohorts. Conversely, because patients treated with ASA were older than those treated by myectomy, unmeasured, age-related confounders, such as comorbid illness, may have been more prevalent in ASA cohorts and may have increased all-cause mortality after septal reduction.

Given the results of previous studies demonstrating an association between left ventricular wall thickness and rates of all-cause mortality and SCD,\textsuperscript{37,42} it was initially surprising that greater preprocedural septal thickness predicted lower all-cause mortality in these cohorts. It should be noted that the evidence associating greater hypertrophy with higher mortality rates is derived mostly from unoperated patients who were not included in the analyzed cohorts. Furthermore, the removal of obstructing, disorganized, and potentially arrhythmic septal myectomy may decrease both all-cause mortality and SCD rates.\textsuperscript{23} Patients with thicker septa who undergo septal reduction treatment also may have a lower risk of complications and a greater potential for hemodynamic benefit.

These meta-analyses have several limitations. First, the duration of follow-up after ASA was much shorter than after surgical myectomy. These comparative mortality rates should be interpreted with the understanding that they are derived from cohorts with different durations of follow-up and under the assumption that postprocedural mortality rates do not change over time. In an ASA cohort of 611 patients and the longest reported clinical follow-up, the estimated rate of all-cause mortality remained linear at 8 years after ASA.\textsuperscript{20} Furthermore, for the variables that predicted all-cause mortality and SCD, constraining the analysis to the ASA studies with the largest follow-up experience (patient-years) did not substantially change the estimated effects. Second, the prevalence of preprocedural clinical risk factors for SCD in patients with HCM was inconsistently reported in the source articles; thus, adjustment for some risk factors for SCD in HCM could not be performed. Third, mortality events were reported on an individual basis, but the timing of deaths was not uniformly reported. Thus, the mortality could be evaluated only at the end of clinical follow-up, and the determination of early versus late mortality events was not feasible. Finally, the unavailability of individual patient characteristics necessitated the combination of cohort data from each study on bloc into larger, pooled aggregates. Therefore, the results of the regression models apply to cohorts rather than individual patients, and the models should not be applied to predict individual patient outcomes. Other statistical methods to account for these differences, such as propensity modeling, could not be applied because of the lack of patient-level data.

In conclusion, based on these extensive systematic reviews, similar low rates of all-cause mortality and SCD were found following either ASA or surgical myectomy for obstructive HCM. However, after adjustment for available baseline characteristics, rates of all-cause and sudden death were lower in ASA cohorts compared with surgical myectomy cohorts, with shorter duration of follow-up in the ASA cohorts. In the absence of randomized trials comparing these procedures, the establishment of a large, prospective, multicenter registry with long-term follow-up could fulfill an unmet need to evaluate outcomes on an individual patient basis.

Disclosures

None.

References


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**CLINICAL PERSPECTIVE**

For patients with obstructive hypertrophic cardiomyopathy and symptoms refractory to medical therapy, septal reduction achieved by either surgical myectomy or alcohol septal ablation (ASA) has been shown to reduce the dynamic left ventricular outflow tract obstruction and reduce symptoms of the disease. However, concerns regarding the possibility of scar-mediated ventricular arrhythmias and sudden cardiac death (SCD) after ASA remain. In the absence of randomized trials evaluating these treatments, this study was performed to compare the rates of overall mortality and SCD reported after these septal reduction therapies. Systematic reviews and meta-analyses of observational studies of surgical myectomy and ASA were performed to derive rates of overall mortality and SCD. Compared with patients treated with ASA, patients treated with surgical myectomy were younger, had greater septal wall thickness, and had longer follow-up. Unadjusted all-cause mortality and SCD rates were similarly low after both septal reduction therapies. After adjustment for baseline characteristics that may influence the rates of these events, ASA-treated cohorts had lower rates of all-cause mortality and SCD than myectomy-treated cohorts. These low rates of overall mortality and SCD after septal reduction may better inform clinical decisions for patients with symptomatic obstructive hypertrophic cardiomyopathy.
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Supplemental Material

Supplemental References

The list of included Alcohol Septal Ablation (ASA) cohorts was modified during the period of data extraction and review. First, one publication was replaced by an updated report from a journal that is not indexed by PubMed. Second, it was decided that an earlier report involving slightly fewer (54 vs. 70) patients should replace a later report since the latter had a substantially shorter period of follow-up (0.5 vs. 3.3 years). Third, through further review of the literature, two additional papers that met the inclusion and exclusion criteria were identified and included. Fourth, since poor or unknown mortality follow-up could invalidate reported mortality data, studies with poor or unknown follow-up were excluded. One study that lacked follow-up data on 67% of patients was excluded. Four studies did not report the percentage of patients with follow-up, and attempts were made to contact their authors. The authors of two of these manuscripts confirmed that no patients were lost to follow-up, and the manuscripts were included. The other manuscripts were excluded because their first authors could not be reached. For one of these manuscripts, an earlier report that had been previously excluded from further analysis because of redundancy did document quality of follow-up, and it was included in place of the later report. Thus, 19 ASA-related publications were included in this analysis (Figure 1).

Supplemental Material